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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,354	11/25/2003	Patrick L. Iversen	50450-8311.US03	8250

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,354	IVERSEN, PATRICK L.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13-15 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,13-15 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 112

2. Claims 1-4, 13-15, and 25-30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record.

3. Applicant's arguments filed 8-08-06 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that:

The *Rochester v. G.D. Searle & Co.,* decision and CAFC's treatment of the result in *Herschler,* that the written description requirement, as it applies to a method of treatment claim, does not require that every possible compound that could be encompassed by the claim must be disclosed in the patent specification. According to Applicants, "[O]n the contrary, *Rochester* seems to suggest that a single compound, that is, any compound that would allow one to practice the claimed invention successful, would be sufficient to meet the written description requirement." Moreover, "[T]he applicant is unaware of any case law or PTO guideline that indicates that a method of treatment claim must disclose every possible or even a plurality of different treatment

compounds in order to meet the written description requirement, nor has the Examiner suggested any such case law."

Contrary to Applicant's assertions, the instant rejection was not based upon a requirement that Applicants disclose every possible or even a plurality of different treatment compounds in order to meet the written description requirement. The instant rejection is based upon the conclusion that Applicants have not shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. No guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed properties, since it is unknown what properties, structural or otherwise, that the antisense oligonucleotides of the present invention must possess for it to reduce the synthesis of a drug metabolizing cytochrome P450 enzyme that reduces the effectiveness of a drug. Moreover, Applicants were not in possession of the full scope of molecules encompassed by the instant claims at the time of filing of the instant application, since it is apparent that further experimentation is required in order to determine the targeting sequences for the full scope of cytochrome p450 enzymes encompassed by the instant claims. Furthermore, additional experimentation would be required to identify the full scope of xenobiotic agents which induce the expression of the full scope of cytochrome P450 enzymes encompassed by the instant claims.

In regards to *University of Rochester v. G.D. Searle,* the court concluded that, as a matter of law, the patent at issue clearly and convincingly proved its own invalidity where the required compound was not disclosed and where there was no pre-existing awareness in the art of a compound exhibiting the claimed activity. Specifically, the court held: "In short, although the '850 patent *(University of Rochester)* describes an assay for determining whether a given compound possesses certain desired characteristics, and identifies some broad categories of compounds that *might* work, these descriptions, without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366....."[T]he '850 patent does not describe the claimed invention in terms that will "enable any person skilled in the art ... to make and use" the invention. At most, its description will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention. That is not enough."

Contrary to Applicant's assertions that: "[*R]ochester* seems to suggest that a single compound, that is, any compound that would allow one to practice the claimed invention successful, would be sufficient to meet the written description requirement," Applicant's characterization of this case is inaccurate since the court held that the '850 patent was invalid since it did not disclose a compound exhibiting the claimed activity, and therefore failed to meet the written description requirements.

Applicant's arguments and/or amendments do not provide evidence that Applicants were in possession of the full scope of the claimed invention at the time the instant invention was filed. As stated in the prior Office Action, although the instant

claims are directed to a method, it is noted that the claimed methods require the use of a broad genus of antisense oligonucleotide compounds that are not sufficiently described in the specification as filed. With the exception of the antisense oligonucleotides having a sequence according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47, absent the need for further experimentation, no guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed properties. The specification as filed does not provide a clear correlation between nucleotide sequence structure, and the ability of the recited antisense oligonucleotides of the present invention to reduce the synthesis of a drug metabolizing cytochrome P450 enzyme that reduces the effectiveness of a drug. As per MPEP § 2163, "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

3. Claims 1-4, 13-15, and 25-30 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cytochrome P450 antisense comprising the administration of the antisense oligomers according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47, or compositions comprising said antisense oligomers, does not reasonably provide enablement for practicing the claimed invention comprising the use of antisense oligonucleotides targeting any cytochrome P450, other than the ones exemplified either *in vivo* (whole animal) or *in*

vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record.

4. Applicant's arguments filed 8-08-06 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by way of amending the claims to encompass the use of PMO's (phosphorodiamidate morpholino oligonucleotides), whose sequences are directed against target RNA encoding a cytochrome p450 enzyme, and specifically, against the AUG translation start site or, where the target is a pre-mRNA, or against a splice site region of the molecule. Moreover, according to Applicants, the two primary arguments advanced by the Examiner are (1) unpredictability in the antisense art and (2) a lack of evidence that cytochrome p450 can metabolize every known conceivable drug. In response Applicants make reference to experimental data Zhang et al. (2006, *in press),* Opalinska et al. (2003), and several Declarations under 37 CFR 1.132 Declarations submitted during the prosecution of other applications. First, Applicants are reminded that as per MPEP §2164.01, the test of enablement "[r]equires a determination of whether *that disclosure, when filed,* contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." The specification as filed did not disclose, nor make reference to the teachings of Zhang et al. (2006, *in press),* or the teachings of Opalinska et al. (2003), or even the results disclosed in the Iversen Declarations under 37 CFR 1.132, in the specification as filed, such that the skilled artisan would have had the guidance provided in these documents,

and would have been able to overcome the known difficulties, and/or hurdles associated with antisense based therapies that were known at the time of filing of the instant application.

In regards to the Iversen Declarations, the experimental data provided were produced as a result of administration of antisense oligomers that are not representative of the full scope of antisense oligonucleotides recited in the instantly claimed invention. Therefore, the experimental data in these Declarations are ineffective to overcome the instant rejection of enablement since the showing is not commensurate in scope with the claims, which reads on the administration of antisense oligomers of undefined nucleotide structure.

Although, the specification does demonstrate the efficacy of the antisense oligonucleotides according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47 in the working examples, no guidance or working examples are disclosed that would allow a skilled artisan to use any other antisense oligonucleotides to inhibit all forms of cytochrome P450 *in vitro* or *in vivo,* nor does the specification as filed teach that the above antisense oligonucleotides can be used to inhibit the metabolism of all drug-metabolizing p450 enzymes. It is noted that the limited disclosure is not sufficient to describe the full scope of antisense oligonucleotides encompassed by, for example claims 1-4, which do not limit the p450 enzyme target. A quick search of the term "cytochrome p450" at Entrez-Nucleotide NCBI: (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide&itool=toolbar), revealed 18,640 hits. Applicants have not provided a clear correlation between the ability of antisense oligonucleotides

according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47 to inhibit the activity of specific variants cytochrome p450, and their ability to inhibit all known variants of cytochrome p450 as suggested by at least claims 1-4. As stated in the prior Office Action, it is well known in the art that identification of target sites in a given mRNA at which antisense oligos bind to cause inhibition of translation, and furthermore produce an *in vivo* therapeutic effect, is an unpredictable art. The skilled artisan would recognize that careful screening of oligonucleotides targeted to different sites on a given mRNA to find oligonucleotide binding sites for inhibition of translation, may fail to identify sites in the 5' untranslated region, the coding region, or in the 3'-untranslated region of the mRNA. The Applicants showing that several antisense oligos were ineffective in inhibiting cytochrome P450 expression, for example oligos according to SEQ ID NO: 16-17, 21-22 and 37-38 exemplify this point, however Applicant's response filed 8-08-06 did not address this issue that was raised in the prior Office Action.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary therapeutic effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In view of Applicant's reliance on post-filing references to support their assertion of enablement of the invention as filed, the breadth of the claimed invention: specifically

in regards to the method reading on the administration of antisense targeting cytochrome p450 enzyme, wherein the scope of the claims includes all variants of cytochrome p450, the lack of sufficient guidance in the specification as filed in regards to the use of morpholino oligomers *in vivo*, and the unpredictability associated with the behavior of an oligomer within a cell as it relates to the sequence composition of the oligomer, it is concluded that undue experimentation would be required to practice the full scope of the claimed invention.

Double Patenting

5. Claims 1-4, 13-15, and 25-30 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of issued US Patent No. 6,686,338, for the reasons of record. It is noted that Applicants did not address the merits of this rejection in the response filed 8-08-06. Applicants provided a terminal disclaimer obviate the double patent rejection of claims 1-9, 13-15, and 25-30 over claims 1-15 of US Patent No. 6,673,778, as set forth in the prior Office Action. However, there was no terminal disclaimer filed over issued US Patent 6,686,338.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit 1633

JLE